

Appl. No. : 10/688,198
Filed : October 17, 2003

AMENDMENTS TO THE SPECIFICATION

Please replace paragraphs [0028], [0029], [0036], [0037], and [0047] with the corresponding rewritten paragraphs below:

-- [0028] One method for generating fully human antibodies is through the use of ~~XenoMouse™~~ XENOMOUSE® strains of mice which have been engineered to contain 245 kb and 190 kb-sized germline configuration fragments of the human heavy chain locus and kappa light chain locus. *See* Green et al. *Nature Genetics* 7:13-21 (1994). The ~~XenoMouse~~ XENOMOUSE® strains are available from Abgenix, Inc. (Fremont, CA). --

-- [0029] The production of ~~the XenoMouse~~ XENOMOUSE® strains of mice is further discussed and delineated in U.S. Patent Application Serial Nos. 07/466,008, filed January 12, 1990; 07/610,515, filed November 8, 1990; 07/919,297, filed July 24, 1992; 07/922,649, filed July 30, 1992; 08/031,801, filed March 15, 1993; 08/112,848, filed August 27, 1993; 08/234,145, filed April 28, 1994; 08/376,279, filed January 20, 1995; 08/430, 938, April 27, 1995; 08/464,584, filed June 5, 1995; 08/464,582, filed June 5, 1995; 08/463,191, filed June 5, 1995; 08/462,837, filed June 5, 1995; 08/486,853, filed June 5, 1995; 08/486,857, filed June 5, 1995; 08/486,859, filed June 5, 1995; 08/462,513, filed June 5, 1995; 08/724,752, filed October 2, 1996; and 08/759,620, filed December 3, 1996 and U.S. Patent Nos. 6,162,963, 6,150,584, 6,114,598, 6,075,181, and 5,939,598 and Japanese Patent Nos. 3 068 180 B2, 3 068 506 B2, and 3 068 507 B2. *See also* Mendez et al. *Nature Genetics* 15:146-156 (1997) and Green and Jakobovits *J. Exp. Med.* 188:483-495 (1998). *See also* European Patent No., EP 0 463 151 B1, grant published June 12, 1996, International Patent Application No., WO 94/02602, published February 3, 1994, International Patent Application No., WO 96/34096, published October 31, 1996, WO 98/24893, published June 11, 1998, WO 00/76310, published December 21, 2000. The disclosures of each of the above-cited patents, applications, and references are hereby incorporated by reference in their entirety. --

-- [0036] Antibodies in accordance with the invention were prepared through the utilization of the ~~XenoMouse~~ XENOMOUSE® strains of mice technology, as described below. Such mice, then, are capable of producing human immunoglobulin molecules and antibodies and are deficient in the production of murine immunoglobulin molecules and antibodies. Technologies utilized for achieving the same are disclosed in the patents, applications, and references disclosed in the Background, herein. In particular, however, a preferred embodiment of transgenic production of mice and antibodies therefrom is disclosed in U.S. Patent Application Serial No. 08/759,620, filed December 3, 1996 and International Patent Application Nos. WO 98/24893, published June 11, 1998 and WO 00/76310, published December 21, 2000, the disclosures of which are hereby incorporated by reference. *See also* Mendez et al. *Nature Genetics* 15:146-156 (1997), the disclosure of which is hereby incorporated by reference. --

-- [0037] Through use of such technology, fully human monoclonal antibodies against a variety of antigens have been produced. Essentially, the ~~XenoMouse~~TM XENOMOUSE® lines of mice were immunized with an antigen of interest, lymphatic cells (such as B-cells) were recovered from the mice that expressed antibodies, the recovered cells were fused with a myeloid-type cell line to prepare immortal hybridoma cell lines, the such hybridoma cell lines were screened and selected to identify hybridoma cell lines that produced antibodies specific to the antigen of interest. --

-- [0047] A hybridoma cell line was created by fusion of B-cells from ~~XenoMouse~~ XENOMOUSE® strains of animals with the non-secretory myeloma, P3X63Ag8.653, cell line (ATCC, cat. # CRL 1580, Kearney et al, J. Immunol. 123, 1979, 1548-1550). After selection of the chosen hybridoma clone, the clone was adapted to serum-free growth conditions using CD-hybridoma (Gibco-Invitrogen) growth medium. For the production of the antibody, cells were grown in stirred tank bioreactors using CD-hybridoma medium supplemented with glucose, glutamine and proteose peptone No 3 (Becton ~~Dikinson~~ Dickinson). Cell culture supernatant was harvested by filtration or centrifugation and passed through a sterile filter prior to being subjected to the pH treatments and activation of enzymatic cleavage. --